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Isomerization, Autoxidation and Epimerization for the Introduction of C-1 to C-5 Functionality into the Taxane ABC Ring System

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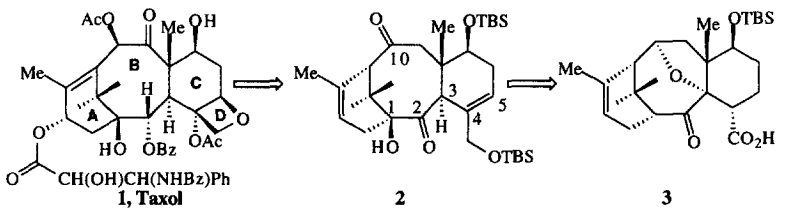
Abstract: Treatment of 2-ketotax-3-enes with *t*-BuOK/*t*-BuOH/THF/65°C results in isomerization of the double bond into the 4,5-position and a trans-B/C ring fusion. Subsequent exposure to *t*-BuOK/THF/O_2/P(OEt)$_3$ introduces the C-1-hydroxyl group.

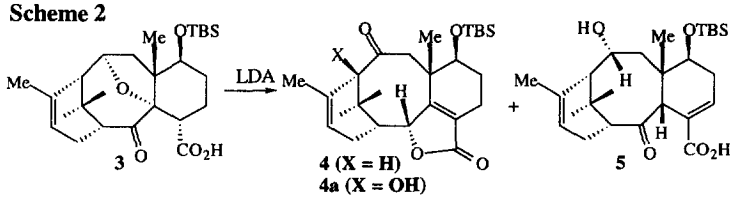
While there have been many strategies reported for the construction of the taxane core structure,[1] and to-date three total syntheses,[2] there is no positive information concerning the introduction of the C-1 hydroxyl group into a taxane molecule with an intact ABC ring system.[3] The strategy we have previously described leads to the acid **3**, **Scheme 1**, which requires further elaboration into **2**.[4] In this letter we describe the conversion of **3** into **2** by C-3 double-bond isomerization to C-4, C-3 epimerization and C-1 autoxidation, thus providing a surprisingly simple solution for the manipulation of this part of the taxane core functionality.

Scheme 1 (Retrosynthetic Analysis of Taxol)



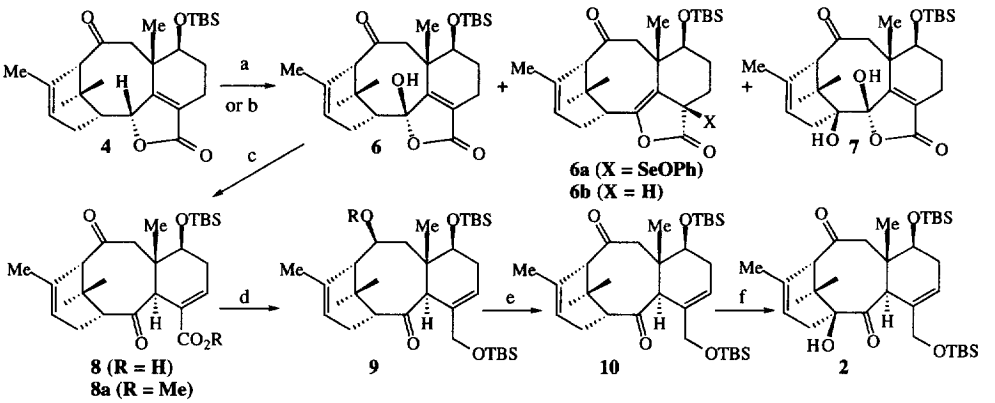
The 3,10-oxido bridge in **3** can be β-eliminated by treatment with LiNPr$_2^i$/THF/3h at 0°C, and is followed by a transannular hydride shift from the C-10 alkoxide to give the butenolide **4** (62%), **Scheme 2.** In principle, the transannular hydride shift should be a reversible reaction. It was found that conducting the above reaction for extended periods (3 days) gave **4** (50%) along with **5** (16%) and traces of **4a** (oxygen leakage).[5] In particular, it should be noted that the B/C rings in **5** are *cis*-fused.

Scheme 2



The butenolide **4** was treated with $(PhSeO)_2O$/*t*-BuOK/$P(OEt)_3$/THF at -0°C and resulted in conversion into the ketal **6** (72%), **Scheme 3**. Small amounts of the selenoxide **6a** and enol-lactone **6b** could also be isolated. Further exposure of **6a/6b** to the oxidation reaction conditions gave **6**. Treatment of **6** with *t*-BuOK/*t*-BuOH/THF at 65°C cleanly gave the C-4 isomer **8**, which was converted into the methyl ester **8a** (47% overall). **Figure 1** shows a Chem 3D representation of **8a** from the X-ray coordinates. When **4** was exposed to the classical autoxidation conditions of *t*-BuOK/THF/O_2/$P(OEt)_3$ [6] it was transformed into **6** (41%) (X-ray) and **7** (47%). The ester **8a** was converted into **9** (R = TBS) by standard reactions and exposed to the autoxidation reaction conditions from -78° to 65°C. No reaction took place! In contrast, oxidation of **9** (R = H) to the 2,10-dione **10**, followed by autoxidation at 52°C gave **2** (31%, 39% based on recovered **10**).

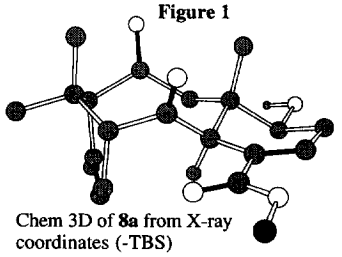
Scheme 3



Conditions:- a) $(PhSeO)_2O$/*t*-BuOK/$P(OEt)_3$/THF/0°C (72%). b) *t*-BuOK/THF/O_2/$P(OEt)_3$/-78°C (**6**, 41% and **7**, 47%). c) i. *t*-BuOK/THF at 65°C. ii. K_2CO_3/THF/MeI (47% from **6**). d). i. DIBAL-H (92%). ii. TBSCl/Et_3N/DMAP/0°C, **9** (R = H) (98%), whereas TBSOTf/Et_3N/0°C gave **9** (R = TBS) (100%). e) Dess-Martin on **9** (R = H) (100%). f) *t*-BuOK/THF/O_2/$P(OEt)_3$/52°C, **2** (31%, 39% based on recovered **10**).

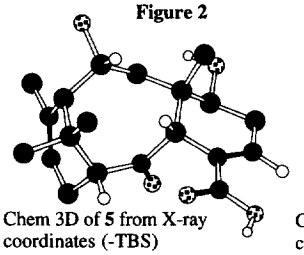
While **5** is a minor product, **Scheme 2**, it was instructive to examine the possibility of introduction of the 1β-hydroxyl group *via* autoxidation of the C-1 enolate. The X-ray structure of **5** shows that the C-1 hydrogen atom is 91° to the adjacent C=O bond, and therefore suitably aligned for enolization, **Figure 2**. The C-3 hydrogen atom is not aligned for enolization (dihedral angle 180°), although upward movement of the C-2 carbonyl group (ca. 20-30°) allows overlap of the C-3 CH σ-bond with the C-2 C=O π-bond.

Figure 1



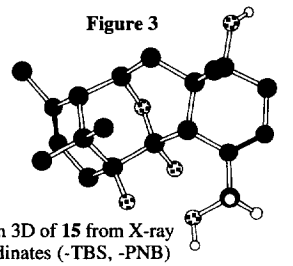
Chem 3D of **8a** from X-ray coordinates (-TBS)

Figure 2



Chem 3D of **5** from X-ray coordinates (-TBS)

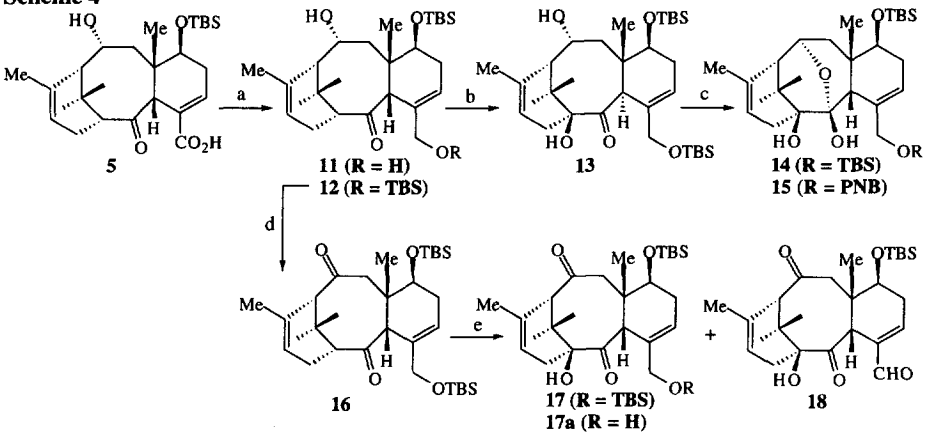
Figure 3



Chem 3D of **15** from X-ray coordinates (-TBS, -PNB)

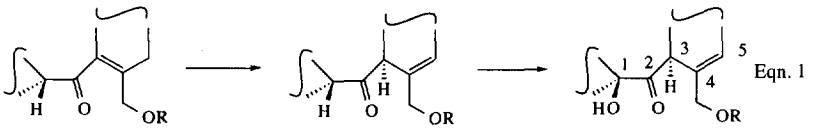
Treatment of **5** with BH_3.THF gave **11** (70%), which was protected as its TBS ether **12** (84%). Exposure of **12** to the standard autoxidation conditions (*t*-BuOK/THF/O_2/P(OEt)3/-78° to 0°C) cleanly gave **13** (50%) and **14** (10%). When **13** was further treated with *t*-BuOK/THF/0°-25°C it was converted into **14** (95%). The derived *p*-nitrobenzoate (PNB) **15** gave crystals suitable for X-ray crystallography, **Figure 3**. Transannular 2,10-ketalization is only possible when the B/C rings are *cis*-fused (C-2, C=O pointing downwards). Consequently, the only logical structure that can be written for **13** is the *trans*-fused B/C stereoisomer. It appears that B/C *cis-trans* isomerization has taken place during the autoxidation reaction.

Scheme 4



Conditions:- a) BH_3.THF (**11**, 70%) followed by TBSCl/Et_3N/DMAP (**12**, 84%). b) *t*-BuOK/THF/O_2/P(OEt)3/-78° to 25°C (50% of **13** and 10% of **14**). c) *t*-BuOK/THF at 0-25°C (>95%). d) Dess-Martin (100%). e) *t*-BuOK/THF/O_2/P(OEt)3/-78° to 25°C, **17** (40%), **17a** (24%) and **18** (34%).

Dess-Martin oxidation of **12** gave **16** (C-3 stereoisomer of **10, Scheme 3**) which upon autoxidation at -78°C gave **17, 17a** and **18**. Under these conditions we did not observe any equilibration of **16** into **10**, nor **17** into **2**.[7]



Eqn. 1

The above transformations, summarized by **Eqn. 1**, conveniently allow for "late" introduction of the 1β-hydroxyl group, *trans*-B/C ring fusion, and the newly positioned C-4,5 double bond is ideally placed for installation of the oxetane. These observations may be useful in provoking shorter synthetic routes to taxanes.

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5. The structures of compounds **4a**, **5**, **6**, **6b**, **7**, **8a** and **15** were elucidated by X-ray crystallography, and the full data are available from the Cambridge X-ray data base.

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7. All new compounds were fully characterized by $^{1}H/^{13}C$ NMR and HRMS.

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